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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,913	DITTRICH ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Claims 12-17 are included in the prosecution.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Claim Objections

3. Claim 12 is objected to because of the following informalities: On line 6 of claim 12, "-35 to 45° C.," should be corrected to "-35 to 45° C,".

4. Claim 13 is objected to because of the following informalities: There is a typo on line 2 of claim 13 which recites: "... wherein the weight ration of ..." The word "ration" should be corrected to "ratio".

5. Claim 17 is objected to because of the following informalities: There is a typo on line 4 of claim 17 which recites: "... are hated to the temperature". The word "hated" should be corrected to "heated".

6. Claim 17 is objected to because of the following informalities: On line 5 of claim 17, "35 to 75° C." should be corrected to "35 to 75° C".

Appropriate corrections are required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 13 recites the weight ratio of "at least one biocompatible plasticizer to biodegradable oligoester is from 1:20 to 9:20". However, the specification discloses "the mass ratio of at least one biocompatible plasticizer to the biodegradable oligoester is from 1:20 to 9:10". The ratio "from 1:20 to 9:20" was not disclosed in the specification.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Chen et al. (J. Microencapsulation, 1999, Vol. 16, No. 5, 551-563).

The claimed invention is a biodegradable antitumor composition with prolonged release of an antitumor agent destined for the administration into tissues, characterized in that it comprises at least one antitumor agent and a carrier, consisting of biodegradable oligoester, having the numeric mean relative molecular mass M_n from 650 to 7,500, the mass mean relative molecular mass M_w from 800 to 10,000 and the

glass transition temperature T_g from -35 to 45°C, and which is prepared by polycondensation reaction of polyhydric alcohol containing at least 3 hydroxy groups with at least one aliphatic α- hydroxy acid in the molar ratio of polyhydric alcohol to aliphatic a-hydroxy acid being from 0.5:99.5 to 12:88, wherein the essential molecule of biodegradable oligoester is a polyhydric alcohol, to the hydroxy groups of which chains created from several molecules of at least one aliphatic a-hydroxy acid are bound by ester bonds, and in that it is in the form of homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion.

Hampl teaches oligoesters, specifically, a terpolymer (GA-M-DLLA) of DL-lactic acid (LA), glycolic acid (GA) and mannitol (MA), a copolymer DL-lactic acid and mannitol (M-DLLA) and lactide-glycolide copolymers (DL-PLGA) (Abstract). The GA-M-DLLA was prepared by the polycondensation reaction (Page 108, 2.2 Preparation of oligoesters) of LA (45.05 mol), GA (45.06 mol) and MA (0.9 mol) and has a T_g of 20°C, M_n of 2.20Kda and M_W of 3.95 kDa (Page 108, Table 1). Bovine serum albumin (BSA) was the active ingredient entrapped in microspheres prepared with the terpolymer of GA-M-DLLA which depicted prolonged release of BSA over 15 weeks (Abstract and Figures 4 and 5). The microspheres were administered subcutaneously to mice (Page 109, 2.6 Biological Experiment).

Hampl does not expressly teach the incorporation of an antitumor active ingredient or compound in the composition comprising a terpolymer prepared by a polycondensation reaction.

Chen teaches injectable carboplatin-loaded poly (D,L-lactic-co-glycolic) acid copolymer (PLGA) microspheres for the intracerebral treatment of malignant glioma (Abstract). "PLGA was selected as the matrix because of its well-established biocompatibility and biodegradation in rat brains ... (and) carboplatin is a potent anticancer agent" (Page 552). Chen teaches that the advantage of incorporating "carboplatin into PLGA and then direct intracerebral delivery to the brain tumour regions can minimize these side effects and improve the efficacy" (Page 552). The PLGA microspheres were prepared by the emulsion/solvent evaporation method (Page 553). Figure 1 shows the prolonged release of carboplatin from the PLGA microspheres (Page 557).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a prolonged release, biodegradable composition with an active ingredient and a terpolymer (GA-M-DLLA - that is prepared by a polycondensation reaction), as suggested by Hampl, combine it with a biodegradable anti-tumor composition comprising PLGA, as suggested by Chen, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Chen teaches that the advantage of incorporating "carboplatin into PLGA and then direct intracerebral delivery to the brain tumour regions can minimize ... side effects and improve the efficacy" (Page 552). One with ordinary skill in the art would substitute the BSA used by Hampl with an active ingredient with anti-tumor properties (such as the carboplatin used by Chen) and use it in the prolonged release, biodegradable

composition comprising oligoesters, with a reasonable expectation of success regarding long term release of the active ingredient.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 12, the biodegradable composition with prolonged release would have been obvious over the biodegradable composition with prolonged release taught by Hampl (Abstract and Page 108, Table 1). The limitation of the antitumor composition and the antitumor agent would have been obvious over the antitumor composition comprising carboplatin taught by Chen (Abstract). The limitation of the "antitumor agent destined for administration into tissues" would have been obvious over the subcutaneous administration of the composition to mice, as taught by Hampl (Page 109, 2.6 Biological Experiment) in view of the antitumor composition comprising carboplatin taught by Chen (Abstract). The limitation of the biodegradable oligoester would have been obvious over the terpolymer (GA-M-DLLA) taught by Hampl (Abstract). The limitation of the M_n from 650 to 7,500, the M_w from 800 to 10,000, and the T_g from -35 to 45°C, would have been obvious over the M_n of 2.20Kda, M_W of 3.95 kDa, and T_g of 20°C, as taught by Hampl (Page 108, Table 1). The limitation of the polycondensation reaction would have been obvious over the GA-M-DLLA that was prepared by polycondensation reaction, as taught by Hampl (Page 108, 2.2 Preparation

of oligoesters). The limitation of the polyhydric alcohol containing at least 3 hydroxy groups would have been obvious over the mannitol in the oligoester taught by Hampl (Abstract). The limitation of the aliphatic α-hydroxy acid would have been obvious over the DL-lactic acid in the oligoester taught by Hampl (Abstract). The molar ratio of the polyhydric alcohol to aliphatic α-hydroxy acid would have been obvious over the ratio of mannitol to DL-lactic acid (0.9:45.05) taught by Hampl (Page 108, Table 1). The limitation of the form of the composition as a homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion would have been obvious over the subcutaneous administration of the composition taught by Hampl (Page 109, 2.6 Biological Experiment) and over the injectable composition taught by Chen (Abstract). One with ordinary skill in the art would formulate the composition for subcutaneous administration or for injection by preparing a homogenous solution or emulsion prior to the administration. This formulation would include modifying the viscosity of the composition in order to optimize delivery of the composition.

11. Claims 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Chen et al. (J. Microencapsulation, 1999, Vol. 16, No. 5, 551-563) and further in view of Berggren et al. (US 5,783,205).

The teachings of Hampl and Chen are stated above.

Hampl and Chen do not expressly teach a composition further comprising a liquid biocompatible plasticizer.

Berggren teaches a drug delivery device (injection) comprising an antibiotic drug and a matrix comprising a bioerodible polymer "selected from polylactic acid, polyglycolic acid, copolymers of lactic acid and glycolic acid, polylactide-co-glycerate, polyglycolide-co-glycerate and poly(orthoesters), or a bioerodible oligomer selected from oligomers of hydroxycarbonic acids and oligomers of glycolic acid and/or lactic acid and their derivatives with alcohols and/or carbonic acids" (Col. 4, lines 48-57). "The delivery device of the invention may also optionally include an amount of a plasticizer to alter the viscosity of the matrix material so that it falls within the range required by the present invention ... Suitable biocompatible plasticizers include ... triethyl citrate, acetyl triethyl citrate ... propylene oxide ... when a plasticizer is included in the matrix material, it is generally present in an amount of from about 5 to about 30 wt %, preferably from about 7 to about 20 wt %" (Col. 9, lines 45-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a prolonged release, biodegradable composition with an active ingredient and a terpolymer (GA-M-DLLA - that is prepared by a polycondensation reaction), as suggested by Hampl, combine it with a biodegradable anti-tumor composition comprising PLGA, as suggested by Chen, and further combine it with the use of a plasticizer in a biodegradable and injectable composition, as taught by Berggren, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Berggren teaches that the use of a plasticizer depends on the matrix material used, for

example for keeping the material from becoming too hard and brittle (Col. 9, lines 48-53).

Regarding instant claims 13-14, the limitations of the one liquid biocompatible plasticizer and the plasticizer soluble in the carrier would have been obvious over the plasticizer used in the matrix material to alter the viscosity, as taught by Berggren (Col. 9, lines 45-67). One with ordinary skill in the art would know that in order to successfully alter the viscosity of the matrix material, the plasticizer used would have to be soluble in the matrix material. The limitation of the weight ratio of the plasticizer to oligoester (claim 13) would have been obvious over the ratio of triethyl citrate to PLGA, which ranges from 1:4.33 to 1:9, as shown in examples 2-5 by Berggren (Col. 13, Table B, lines 55-63).

Regarding instant claim 15, the limitation of an agent influencing the kinetics of the release of the antitumor agent would have been obvious over the "drug release-rate regulating agents" taught by Berggren (Col. 10, lines 1-2).

Regarding instant claim 16, the limitation of a stabilizer of the antitumor agent or carrier would have been obvious over the stabilizers taught by Berggren (Col. 10, lines 1-3).

Regarding instant claim 17, the limitation of heating an antitumor agent, a carrier, optionally a plasticizer, an agent influencing the kinetics of the release of the antitumor agent, and a stabilizer of the antitumor agent or a stabilizer, would have been obvious over the composition taught by Hampl, in view of the antitumor agent taught by Chen, and further in view of the teaching by Berggren that the "matrix material is heated to

soften the material to a point where it becomes flowable and can be delivered at a physiologically compatible elevated temperature into a biological pocket" (Col. 4, lines 14-17). One with ordinary skill in the art would heat the mixture depending on the constituents (polymer matrix, active ingredient) and depending on the administration site. The recited temperature range of 35 to 75°C would have been an obvious variant during the process of routine experimentation, unless there is evidence of criticality or unexpected results.

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

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